The Linkage Relation of the Loci for the Xm Serum System and the X-linked Form of Hurler's Syndrome (Hunter's Syndrome)

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The Xm serum system (Berg and Bearn, 1966*a*) was discovered by means of an immune serum produced in a rabbit. After proper absorption, this antiserum reacted to form a precipitate with some, but not all, human sera when the agar gel double-diffusion technique (Ouchterlony, 1958) was employed. About twice as many females as males possessed the demonstrated antigen in their serum, and family studies gave strong evidence that the demonstrated antigen was inherited as an X-linked, dominant trait. Preliminary linkage studies indicated that the *Xm* locus is probably within measurable distance of the loci for hemophilia B, hemophilia A, and deutan color vision, but is probably far away from the locus for the Xg blood-group system (Berg and Bearn, 1966*b*).

The Hunter syndrome (the X-linked variant of the Hurler syndrome) is inherited as an X-linked, recessive trait. Recent progress in tissue-culture techniques (Danes and Bearn, 1965, 1966) has, however, made it possible to recognize the heterozygous female carriers of the Hunter gene. These techniques have significantly increased the amount of information it is possible to extract from linkage studies on this disease, as the genotype of girls can be scored. This is of some importance because the disease is very uncommon, and it is difficult to collect a large number of families for linkage studies.

Very little is known about the location of the Hunter locus on the X chromosome. The purpose of this paper is to report a search for linkage between the locus for the Xm serum system and the locus for the Hunter syndrome.

MATERIALS AND METHODS

Hunter Patients and Their Families

All the families were ascertained on the basis of their having at least one child affected with the Hunter syndrome, and they were referred to us by a number of physicians, to whom we wish to express our gratitude. The healthy female family

Received December 26, 1967.

Supported in part by a grant from The National Foundation and by U.S. Public Health Service grant AM 11796.

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members were classified as carriers or noncarriers of the Hunter gene by tissue-culture methods (Danes and Bearn, 1965, 1966).

Typing for the Xm Factor

Fresh sera from the patients and their family members were typed for the Xm(a) antigen employing the technique described previously (Berg and Bearn, 1966*a*). The original anti-Xm(a) serum from one single rabbit was used.

Linkage Analyses

Morton's (1955) *lod* score method, employing the detailed instructions of Maynard-Smith *et al.* (1961), was used. No a priori correction (Renwick and Schulze, 1964) was applied.

RESULTS

Four family groups were found to give information on possible linkage between the *Xm* and *Hunter* loci. These four families are shown in Figure 1. Only informative parts of the pedigrees have been included in the illustration. In family No. 4, at least one of the children must be the result of a crossover in the mother. Other direct evidence of crossing over was not found. The *lod* scores at different values of the recom-

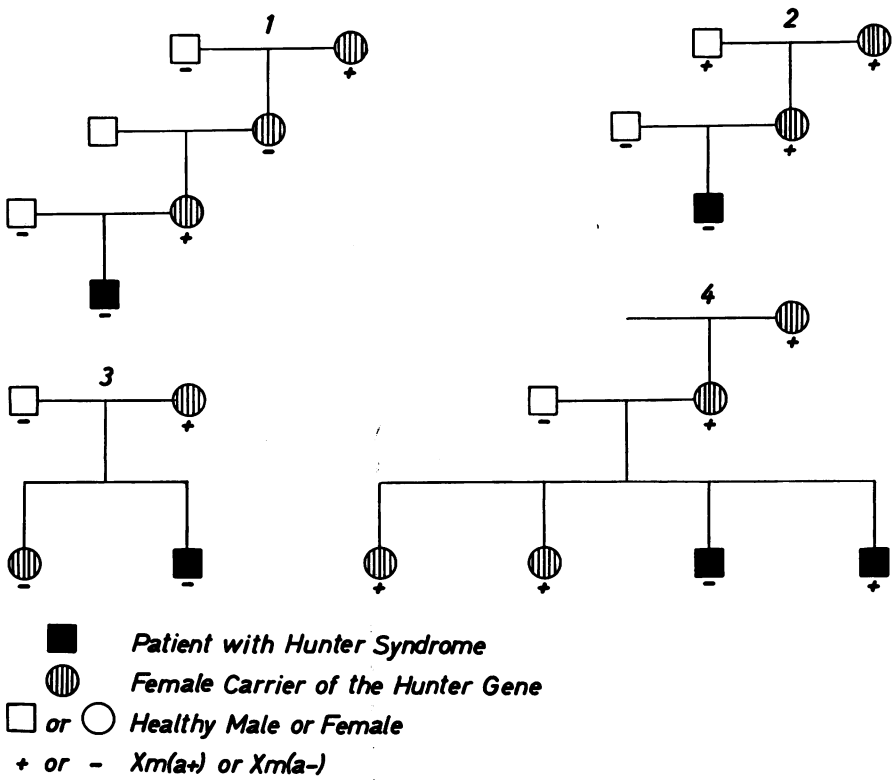

FIG. 1.—Segregation of *Xm* and *Hunter* genes in four families

bination fraction for each of the four families as well as the total *lod* scores for all the families are shown in Table 1. The data exclude very close linkage. The curve of relative probabilities of different values of the recombination fraction is shown in Figure 2. The peak of the curve corresponds to a recombination fraction of about 0.09. Thus, from the present data, the best estimate of the recombination fraction between

TABLE 1

XM AND HUNTER SYNDROME: THE *lod* SCORES

FAMILY NO.	SCORING	RECOMBINATION FRACTION, θ						
		0.00	0.05	0.10	0.20	0.30	0.40	0.50
1.....	1 nonrecombinant	0.301	0.279	0.255	0.204	0.146	0.079	0.000
2.....	1 nonrecombinant	0.301	0.279	0.255	0.204	0.146	0.079	0.000
3.....	Z_1 (0:2)e_1(2:0)	0.477	0.395	0.319	0.190	0.088	0.023	0.000
4.....	Z_1 (3:1)e_1(4:0)	$-\infty$	−0.265	−0.084	0.012	0.019	0.006	0.000
Sum of *lod* scores.....		$-\infty$	0.688	0.745	0.610	0.399	0.187	0.000
Antilog-relative probabilities of θ.....		.....	4.875	5.559	4.074	2.506	1.538	1.000

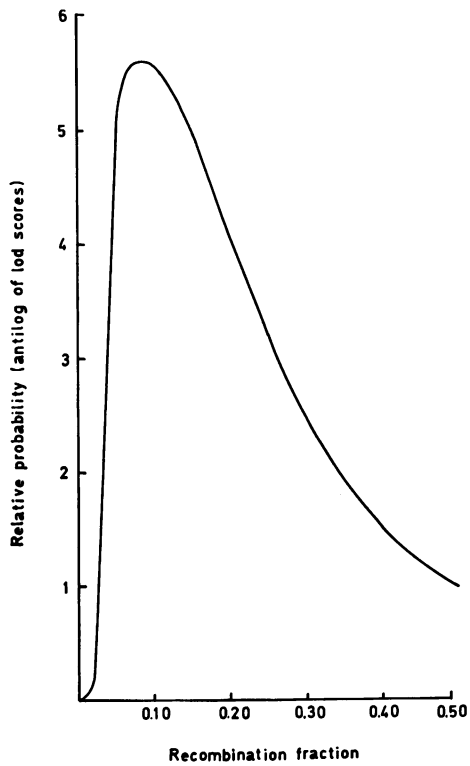

FIG. 2.—The Hunter syndrome and the Xm serum system: Relative probabilities of various recombination fractions.

the *Xm* and *Hunter* loci is 0.09, but the confidence limits are wide; the 90% confidence limits are 0.05 and 0.44, and the 95% confidence limits are 0.04 and 0.47.

DISCUSSION

The present material is small, and conclusions must therefore be drawn with caution. Family No. 4 should be particularly mentioned in this connection. If the mother has the Xm^a and *Hunter* genes in coupling, there will be one recombinant and three nonrecombinants among the children. If, however, the mother has the Xm^a gene and the *Hunter* gene in repulsion, there will be three recombinants and only one nonrecombinant in this same family. Given these reservations, however, it may be concluded that the present data suggest that the *Xm* locus and the *Hunter* locus are within measurable distance of each other. The difficulties in collecting a large number of families in which the Hunter gene segregates justify the reporting of the present limited material.

The suggestion of the present investigation could be verified, or contradicted, if extensive linkage data could be obtained for the relation between the *Hunter* locus and any third locus on the X-chromosome, provided the linkage relation between the *Xm* locus and this third locus were known. Although the difficulties in obtaining extensive linkage data for the Hunter syndrome are formidable, the present study illustrates that linkage data can be obtained with great efficiency now that it is possible to score heterozygotes for the Hunter gene.

SUMMARY

The results of testing members of families in which the Hunter gene segregates for the Xm(a) serum antigen suggest that the *Hunter* locus and *Xm* locus are within measurable distance of each other. The present best estimate of the recombination fraction is 0.09. The confidence limits are, however, wide because of the limited material.

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